TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results					Comments
Mills, 1950, U.S.A. (*167*).	118 male and female patients with pneumonia and 472 healthy individuals from "random" sample.	Hospital Interview.		*Cases*	*Controls*			The author stated that there was a significant difference in tobacco usage between the two groups.
			Mean age	49.6	49.6			
			NS	15.25	25.21			
			Cigarettes only	63.56	52.33			
			Mixed	21.19	22.46			
Lowe, 1956, England (*157*).	520 male and 185 female tuberculosis patients and 419 male and 249 female control outpatients.	Interview by trained social worker.		*Males*		*Females*		Cigarette smokers include pipe smokers. The author noted a significant deficiency of non- and light smokers and an excess of heavy smokers among the cases
				Cases	*Controls*	*Cases*	*Controls*	
			NS	2.5	8.1	37.3	51.4	
			Cigarettes/day: 1–9	9.2	12.9	20.5	25.7	
			10–19	38.1	35.6	30.8	20.5	
			20–29	29.4	27.4			
			30–39	11.3	9.3	11.4	2.4	
			>40	9.4	6.7			
Dowling, et al., 1957, U.S.A. (*72*).	Individuals exposed to "infectious cold agent" and placebo.	Interview and medical examination.		*Exposed to placebo*		*Exposed to infectious agent*		No statistically significant differences noted.
				Number	*Percent developing "cold"*	*Number*	*Percent developing "cold"*	
			NS	111	10	328	34	
			SM	78	14	249	35	

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results				Comments
Boake, 1958, U.S.A. (*33*).	Parents of 59 families.	Interview		*Person-years*	*Number of respiratory illnesses*	*Illnesses/person-years*	No statistically significant differences noted.
			NS .... (24)	120	624	5.2	
			Cigarettes/day: 1–10 .... (19)	99	529	5.3	
			11–20 .... (25)	108	486	4.5	
			>20 .... (19)	99	424	4.3	
			Pipe, cigar .... (14)	72	304	4.2	
Shah et al., 1959, India (*205*).	Tuberculosis institute employees.	Survey, X-ray, and interview.		*Tuberculous by X-ray*	*Normal or nontuberculous*		† Numbers in parentheses represent figures "expected" by use of 2 x 2 contingency table. Tuberculous employees were found to have significantly fewer nonsmokers and more smokers.
			NS	†10 (19.7)	178 (168.3)		
			SM	36 (26.3)	215 (224.7)		

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results				Comments
Brown et al., 1961, Australia (*4*).	306 male and female tuberculosis clinic patients, 221 male and female outpatients.	Interview	*Smoking habits prior to diagnosis*				Data presented only on Queensland sample. The authors noted that the significant difference between the patients and controls was not present when the groups were matched for alcohol intake.
				Tuberculous patients (percent)	*Controls (percent)*		
			NS	9.1	19.9		
			Cigarettes/day: 1–9	10.5	15.4		
			10–19	34.3	19.5		
			20–29	26.3	25.8		
			30–39	7.2	5.4		
			>40	6.2	9.1		
			Pipes	5.9	4.6		
Haynes et al., 1966, U.S.A. (*108*).	191 male prep school students.	Interview	*Average number of respiratory illnesses/10 students (adjusted for age)*				
				All respiratory episodes	*All severe respiratory episodes*	*All severe lower or combined respiratory episodes*	
			NS (99)	11.1	1.6	0.36	
			SM (92)	20.2	6.7	3.34	
Parnell et al., 1966 Canada (*181*).	47 smoking-nonsmoker pairs of student nurses matched for age and parents' occupational class.	Interview and health service records.	*Median number of illnesses/student*				The authors noted that these differences were statistically significant. † Particularly tracheitis, bronchitis, and pneumonia.
				All respiratory diseases†	*All other illnesses*		
			NS (47)	2.08	2.99		
			SM (47)	2.54	5.00		

TABLE A15.—*Studies concerning the relationship of smoking to infectious respiratory disease in humans (cont.)*

(Actual number of cases shown in parentheses)

SM = Smokers NS = Nonsmokers

Author, year, country, reference	Number and type of population	Data collection	Results	Comments
Peters et al., 1967, U.S.A. (*183*).	1,496 Harvard and 370 Radcliffe students.	Medical history, chart review, and questionnaire.	*Number of visits to student health unit for respiratory illness/student (common colds, pharyngitis, bronchitis, laryngitis, pneumonia—not allergic rhinitis)* *Harvard* / *Radcliffe* NS .... 1.44 (771) / 1.44 (193) SM .... †2.27 (725) / 2.27 (177) <2 years smoked .... 2.00 3–4 .... 2.30 >5 .... 2.50	† p<0.001.
Finklea et al., 1969 U.S.A. (*83*).	1,811 male college students.	Questionnaire prior to A_2/HK/68 epidemic and follow-up on morbidity.	Heavy smokers—21 percent more clinical illnesses than nonsmokers; 20 percent more requiring bed rest than nonsmokers Light smokers—10 percent more clinical illnesses than nonsmokers; 7 percent more requiring bed rest than nonsmokers.	The authors also noted that: (a) Smokers exhibited serologic evidence of increased subclinical A_2/HK/68 infection. (b) There was no difference in the vaccination status between smokers and nonsmokers.

TABLE A16.—*Complications developing in the postoperative period in patients undergoing abdominal operations*

Group	Cases	Percent chest clear	Percent bronchitis	Percent broncho-pneumonia and atelectasis	Percent total complication rate
Men over 20					
Smokers	300	41.7	53.0	5.3	58.3
Light Smokers	180	68.4	27.7	3.9	31.6
Nonsmokers	66	92.5	6.0	1.5	7.5
Women over 20					
Smokers	23	39.1	43.5	17.4	60.9
Light Smokers	62	77.5	20.9	1.6	22.5
Nonsmokers	518	88.8	8.1	3.1	11.2

SOURCE: Morton, H. J. V. (*173*)

TABLE A17.—*Arterial oxygen saturation before and after operation*

Group	Case number	Before operation	Day 1	Day 2	Day 3
Arterial oxygen saturation (percentage)					
	1	94	93	94	..
	2	94	93	94	..
Nonsmokers	3	96	93	94	..
	4	95	90	94	..
	5	94	90	93	..
	6	95	91	89	91
	7	92	89	81	89
Smokers	8	91	89	85	89
	9	93	91	88	92
	10	90	87	88	92

SOURCE: Morton, A. (*172*).

CHAPTER 4

Cancer

Contents

FIGURES

LIST OF TABLES

LIST OF TABLES (Continued)

(A indicates tables located in appendix at end of chapter)

(A indicates tables located in appendix at end of chapter)

INTRODUCTION

During the early years of this century, a number of pathologists and clinicians reported a dramatic increase in the incidence of lung cancer. Autopsy studies and studies of lung cancer death rates revealed a significant increase beginning prior to World War I and continuing during the ensuing years. This epidemic of lung cancer continues to the present day, with nearly 60,000 deaths expected from this disease in the United States during 1970.

Beginning in the 1920's, a number of reports appeared which suggested a relationship between lung cancer and tobacco smoking (*4, 203, 278*). Since that time, many clinical and epidemiological studies have been published which confirm this relationship. The 1964 Report (*291*) contains a thorough review and analysis of the data available at that time as well as an excellent discussion of the considerations necessary for their evaluation.

Major epidemiological studies have demonstrated that smokers have greatly increased risks of dying from lung cancer compared to nonsmokers. An increased risk of lung cancer has been found for every type of smoking habit investigated, but two characteristics of the risk are particularly evident: The risk is much greater for cigarette smokers than for smokers of pipes and cigars, and among cigarette smokers a dose relationship exists. That is, the more one smokes, as measured by total pack-years of smoking, present level of smoking, degree of inhalation, or age at start of smoking, the greater is the risk. It has also been shown that the risk of lung cancer among ex-smokers decreases with time almost to the level of nonsmokers; the time required is dependent on the degree of exposure prior to cessation.

Pathologists have found that the squamous cell or epidermoid form of lung cancer is the most prevalent one in cigarette smoking populations and that this form accounts for a major portion of the rise in lung cancer deaths (*154*). Such studies have also indicated a lower prevalence among smokers for oat-cell and adenocarcinomas of the lung than for the squamous form, but in most studies a higher frequency of these tumors is found among smokers than among nonsmokers.

Smoking has been implicated in the development of other types of cancer in humans. Among these is cancer of the larynx. A number of epidemiological studies have demonstrated increased mortality rates for laryngeal cancer in smokers, particularly cigarette smokers, compared with nonsmokers. Autopsy studies have revealed that a clear dose-relationship exists between smoking and the development of cellular changes in the larynx, including carcinoma *in situ*.

Cancers of the mouth and oropharynx have been found to be more common among users of all types of tobacco than among abstainers. Although smoking is a definite risk factor in the development of malignant lesions of the oral cavity and pharynx, its relative contribution in conjunction with other factors such as poor nutrition and alcohol consumption has not been fully clarified.

Similarly, although smokers are more likely to develop carcinoma of the esophagus than nonsmokers, the relative additional contribution of smoking in conjunction with nutritional factors and alcohol consumption requires clarification.

Smokers have been found to be more at risk for the development of cancer of the urinary bladder than are nonsmokers, and there is evidence to suggest that some smoking-induced abnormal metabolic product or abnormal concentration of a metabolic product may be responsible for this increased risk. In addition, cancer of the kidney is apparently more common in smokers than in nonsmokers, but the epidemiologic evidence for this relationship is not as definite as for bladder cancer.

Epidemiological studies have indicated an association between smoking and cancer of the pancreas. The significance of this relationship is unclear at this time.

Experimental studies have demonstrated the carcinogenicity of the condensate of tobacco smoke, or "tar." This material, when painted on the skin of animals, leads to the development of squamous cell tumors of the skin. Researchers have shown that this condensate contains substances known as carcinogens, capable of inducing cancers. Among these carcinogens are several chemicals which have been identified as tumor initiators, that is, compounds which initiate changes in target cells and also tumor promoters, or compounds which promote the neoplastic development of initiated cells. Other, as yet unidentified, factors are presumably also involved because the sum of the carcinogenic effects of the known agents does not equal that of cigarette smoke condensate.

Numerous experiments have been performed in which whole cigarette smoke, filtered smoke, or certain constituents of smoke, such as the "tar," are administered by varying methods to animals or to tissue and cell cultures in order to investigate the neoplastic-inducing properties of cigarette smoke. Particular difficulty has been encountered in experiments which have attempted to deliver whole cigarette smoke to the larynx and into the lungs of experimental animals. This has resulted in the use of other methods such as the implanting of pellets containing suspected carcinogens and the instilling into the trachea of suspected carcinogens as such, or adsorbed onto fine inert particulate matter as a carrier. The difficulty with the inhalation studies has been twofold. First, the animals, particularly the smaller species such as the rat, frequently die from the acute toxic effects of the nicotine and carbon monoxide in the tobacco smoke. Second, the upper respiratory tract of experimental animals, particularly the nose, is much different from analogous human structures, resulting in a more efficient filtration of smoke in the upper respiratory tract. Nevertheless, in rodents and canines, progressive changes apparently indicative of ultimate neoplastic transformation have been identified in the respiratory tract.

Recently, two studies in different species and in different target organs have been reported concerning the development of early invasive cancer following the prolonged inhalation of cigarette smoke. Auerbach and his coworkers (*11*) trained dogs to inhale cigarette smoke through a tracheostoma. After approximately 29 months of daily exposure, these investigators found a number of cancers of the lung.

Dontenwill (*76*) in the second of these two studies, exposed hamsters to the passive inhalation of cigarette smoke over varying and prolonged periods of time. He observed the development of premalignant changes and, ultimately, invasive squamous cell cancer of the larynx.

LUNG CANCER

Cancer of the lung in the United States accounted for 45,383 deaths among males and 9,024 deaths among females in 1967 (*289*). It is presently estimated that approximately 60,000 people will die of lung cancer during 1970.

The alarming epidemic of lung cancer is a relatively recent phenomenon. Death rates for lung cancer (ICD Codes 162, 163) rose from 5.6 (per 100,000 resident population per year) in 1939 to 27.5 in 1967 (*289, 290*). This rapid increase followed the increased use of cigarettes among the United States population. The increase has occurred principally among males, although more recently females have shown a similar rising pattern.

The converging evidence for the conclusion that cigarette smoking is the major cause of lung cancer is derived from varied types of research including epidemiological, pathological, and laboratory investigations.

Numerous epidemiological studies, both retrospective and prospective, have been carried out in different parts of the world to investigate the relationship between smoking and cancer of the lung. These studies are outlined in tables 1, 2, A3, and A4.

Prospective Studies

The major prospective studies concerning the relationship of smoking and lung cancer are presented in table 1. In all, these investigations have studied more than a million persons from a number of different populations for up to 10 years. These studies show increased lung cancer mortality ratios for cigarette smokers of all amounts ranging from 7.61 to 14.20 among male smokers as compared to nonsmoking males. The one major prospective study of female cigarette smokers reveals an overall mortality ratio of 2.20 (*118*).

Also uniformly present in these studies is a dose-related increase in the mortality from lung cancer with increasing amounts of cigarettes smoked per day. Other measures of exposure show similar trends. Hammond (*118*) reported increased mortality ratios associated with increased inhalation (table 1) as well as with increased duration of smoking (table 2).

Ex-smokers show significantly lower lung cancer death rates than continuing smokers. In their study of more than 40,000 British physicians, Doll and Hill (*74, 75*) noted a decrease in lung cancer mortality rates with increasing time since smoking stopped (table 1). During the past 20 years, half of all the physicians in Britain who used to smoke cigarettes have stopped smoking. While the death rates from lung cancer rose by 7 percent among all men from England and Wales during the period from 1953–57 through 1961–65, the rates for male doctors of the same ages fell by 38 percent (*96*).

Pipe and cigar smokers have been shown in the prospective studies to have lung cancer mortality rates higher than those of nonsmokers, although these are generally substantially lower than those of cigarette smokers (table 1).

Retrospective Studies

More than 30 retrospective (case-control) studies have been reported concerning the relationship of smoking and lung cancer. These studies are outlined in tables A3 and A4. Table A4 presents the percent of nonsmokers and of heavy smokers among both cases and controls as well as the relative risk ratios for all smokers.

TABLE 1.—*Lung cancer mortality ratios*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Prospective studies									
Author, year, country, reference	Number and type of population	collection Data	Follow-up years	Number of deaths	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 States ages 50–69.	Question-naire and interview.	3½	448 SM . 443 NS . 15	NS ..... 1.00 (15) <10 .... 8.00 (24) 10–20 ...10.50 (84) >20 ....23.40 (117) All ....†10.73 (397)	*Pipe* NS ... 1.00 (15) SM ... 2.57 (18) *Cigar* NS ... 1.00 (15) SM ... 1.00 (7)	No data	*Bronchogenic* (*Excluding adenocarcinoma*) Never smoked .... 1.00 *Previously <1 pack/day* Continuing ....16.94 Duration of cessation: <1 year ..16.50; 1–10 years .10.44; >10 years .. 1.51 *Previously >1 pack/day* Continuing ....46.21 Duration of cessation: <1 year ..58.23; 1–10 years .22.82; >10 years ..17.79	341/448 deaths with microscopic proof. In-cludes those regular cigarette smokers who also smoked pipes and cigars. † With or without microscopic proof.
Doll and Hill, 1964, Great Britain (*74*).	Approxi-mately 41,000 male British physicians	Question-naire and followup of death certificate.	10	212 SM . 209 NS . 3	NS ..... 1.00 (3) 1–14 .... 8.14 (22) 15–24 ...19.86 (53) >25 ....32.43 (57)	*Pipe and Cigar* NS.... 1.00 (3) *Grams/day* 1–14.. 6.00 (12) 15–24.. 6.43 (6) >25...13.71 (3)	No data	*Cigarette smokers* NS .... 1.00 (3) Continuing ....18.29 (124) Duration of cessation: <5 years .. 9.57 (5); 5–9 years . 7.00 (7); 10–20 years . 2.57 (3); >20 years . 2.71 (2)	
Best, 1966, Canada (*21*).	Approxi-mately 78,000 male Canadian veterans.	Question-naire and followup of death certificate.	6	331 †SM . 324 NS . 7	NS ..... 1.00 (7) <10 ....10.00 (57) 10–20 ...16.41 (204) >20 ....17.31 (63) All 14.20 (245)	*Pipe* NS ....1.00 (7) SM ....4.35 (18) *Cigar* NS ....1.00 (7) SM 2.94 (2)	No data	NS .... 1.00 (7) Ex-smokers of cigarettes only 6.06 (18)	† Refers to cur-rent cigarette smokers only.

TABLE 1.—*Lung cancer mortality ratios (cont.)*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Prospective studies

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Kahn	U.S. male	Question-	8½	1,256		*Pipe*			
(Dorn),	veterans	naire and		SM .1,178	NS 1.00 (78)	NS 1.00 (78)	No data		
1966,	2,265,674	followup		NS . 78	1–9 .... 5.49 (45)	SM 1.84 (17)		NS 1.00 (78)	
U.S.A.	person	of death			10–20 ... 9.91 (303)	*Cigar*		*Number of cigarettes/day:*	
(*139*).	years.	certificate.			21–39 ...17.41 (315)	NS 1.00 (78)		1–9 .... 0.95 (4)	
					>39 ....23.93 (82)	SM 1.59 (6)		10–20 .... 3.48 (39)	
					All 12.14 (749)	*Pipe and cigar*		21–39 .... 9.33 (57)	
						NS 1.00 (78)		>39 .... 8.24 (19)	
						SM 1.66 (20)			
Hammond,	440,558	Interviews	4	*Males*	*Current cigarettes*	*Pipe*	*Males*		ICD code
1966,	males	by ACS		1,159	*only*	NS 1.00 (49)	NS 1.00 (49)		162 only.
U.S.A.	562,671	volunteers.		SM .1,110	*Males*	SM 2.24 (21)	Slight 8.42 (120)		
(*118*).	females			NS . 49	NS 1.00 (49)	*Cigar*	Moderate ...11.45 (311)		
	35–84			*Females*	1–9 .... 4.60 (26)	NS 1.00 (49)	Deep 14.31 (141)		
	years of			183	10–19 ... 7.48 (82)	SM 1.85 (22)	*Females*		
	age in 25			SM . 81	20–39 ...13.14 (381)	*Pipe and cigar*	NS 1.00 (102)		
	States.			NS . 102	>40 ....16.61 (82)	NS 1.00 (49)	Slight 1.78 (25)		
					All 9.20 (719)	SM 0.90 (11)	Moderate } .. 3.70 (45)		
					Females		Deep }		
					NS 1.00 (102)				
					1–19 .... 1.06 (20)				
					>20 .... 4.76 (50)				
					All 2.20 (81)				

TABLE 1.—*Lung cancer mortality ratios (cont.)*

(Actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Regular cigarette smoking only (cigarettes/day)	Pipe cigar	Inhalation	Exsmokers	Comments
Prospective studies									
Buell et al., 1967, U.S.A. (*49*).	69,868 American Legionnaires 35–75 years of age and older.	Questionnaire and followup of death certificate.	3	304	NS .... 1.00 <20 .... 2.30 20 ... 3.50 >20 .... 4.90				
Hirayama, 1967, Japan (*125*).	265,118 male and female adults 40 years of age and older.	Trained PHS nurse interview and followup of death certificate.	1½	43 SM . 40	NS ..... 1.00 (3) 1–24 ... 2.69 (29) >25 .... 5.68 (5)				Preliminary report.
Weir and Dunn, 1970, U.S.A. (*306*).	68,153 males in various occupations in California.	Questionnaire and followup of death certificate.	5–8	368	NS .... 1.00 ±10 .... 3.72 ±20 .... 9.05 >30 .... 9.56 All 7.61				NS include pipe and cigar smokers SM include ex-smokers.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or exsmokers.

TABLE 2.—*Lung cancer mortality ratios for males by duration of cigarette smoking*
(Actual number of deaths are shown in parentheses)

Age began cigarette smoking	35–54	55–69	70–84	35–84
25 or older	2.77 (5)	3.39 (12)	3.38 (3)	3.21 (20)
20–24	5.83 (31)	11.11 (72)	12.11 (7)	9.72 (110)
15–19	8.71 (112)	13.06 (176)	19.37 (27)	12.81 (315)
<15	12.80 (35)	15.81 (57)	16.76 (9)	15.10 (101)

SOURCE: Hammond, E. C. (118).

These smoker-nonsmoker risk ratios range from 1.2 to 36.0 for males and from 0.2 to 5.3 for females.

Although not presented in tabular form, the data concerning lung cancer and pipe or cigar smoking are similar to those found by the prospective studies mentioned above. However, a study by Abelin and Gsell (*1*) conducted on a rural Swiss population noted that an increased risk of lung cancer was present among heavy cigar and pipe smokers (as well as cigarette smokers) to a greater degree than previously reported. The authors suggest that their findings might be due to differences in either the amount smoked or the carcinogenicity of Swiss and German cigars. The difference might also be explained by the greater use and more frequent inhalation of small cigars in Switzerland as compared to other countries where large cigars are more commonly smoked but rarely inhaled. Kreyberg (*154*), in a review of 887 cases of lung cancer in Norway, noted that pipe smokers showed an increased risk of lung cancer, although this risk was substantially lower than that for cigarette smokers.

LUNG CANCER TRENDS IN OTHER COUNTRIES

Several studies of particular interest are those in which the changing mortality from lung cancer has been investigated in countries in which cigarette smoking has become popular and widespread only in recent years. In those countries where accurate statistics for lung cancer mortality are available for both the pre-smoking and post-smoking periods, long-term trends can be studied in some detail.

Two such studies have dealt with lung cancer mortality trends in Iceland. Dungal (*83*) noted in 1950 that lung cancer was a rare disease in Iceland and felt that this rarity could be explained by the relatively late onset of heavy tobacco smoking in the Icelandic population when compared to that of Great Britain and Finland. He observed that the annual per capita consumption of tobacco did not reach one pound in Iceland until 1945, while Great Britain and Finland passed that amount before 1920. In 1967, Thorarinsson, et al. (*276*) noted a sharp rise in the incidence of lung cancer in Ice-

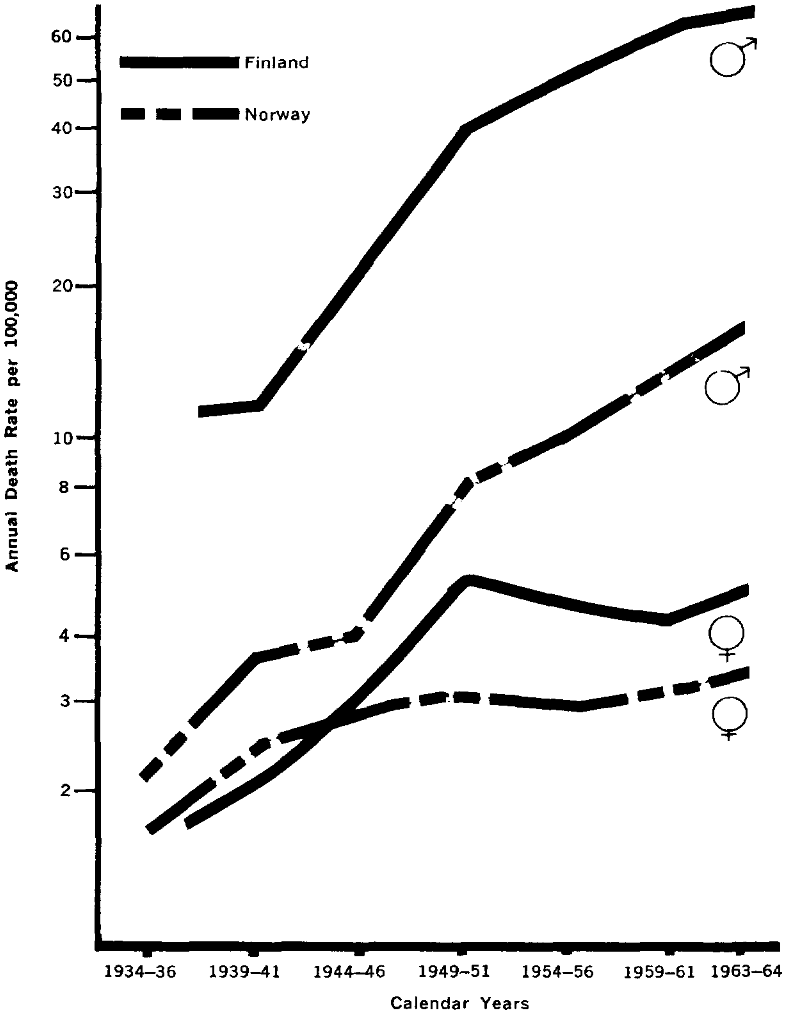

FIGURE 1.—Lung cancer, Finland and Norway.
SOURCE: Kreyberg, L. (154).

land after 1950 and found a correlation between that increase and the increasing sale of cigarettes in that country.

Kreyberg (*154*) analyzed the lung cancer death rates of both Norway and Finland in relation to the use of tobacco in those two countries over the past 100 years. Figure 1 shows the substantial difference in lung cancer mortality between the two countries. Kreyberg observed that cigarettes came into use in Norway in 1886 while the Finnish population (more closely allied to Russia socioeconomically) was consuming more than 100 million cigarettes per year during the decade of the 1880's. Cigarettes remained scarce in Norway until after World War I, and this 30-year lag in consump-

TABLE 5.—*Annual means of total lung cancer mortality and sex ratios for selected periods in Finland and Norway*

Year	Finland		Norway	
	Males	*Females*	*Males*	*Females*
1936–38	192	33	34	30
Sex ratio	5.8 : 1		1.1 : 1	
1963–65	1,319	121	355	79
Sex ratio	10.9 : 1		4.5 : 1	

SOURCE: Kreyberg, L. (154).

tion behind that of Finland is reflected in a similar lag in total lung cancer mortality and sex ratios (table 5).

HISTOLOGY OF LUNG TUMORS

A number of investigators have focused their interest upon the relationship of cigarette smoking to the varied histology of lung tumors. The major histological types of lung cancer include squamous cell (epidermoid) carcinoma, small and large cell anaplastic carcinomas, adenocarcinoma (including bronchiolar and alveolar types), and undifferentiated carcinoma (*153*). A review of these studies (table 6) indicates a closer relationship between cigarette smoking and epidermoid carcinoma than between cigarette smoking and adenocarcinoma (*42, 113*).

The work of Kreyberg (*153*) in Norway, over the past 20 years, provides evidence of a specific histologic relationship. This investigator noted that a clearer association is obtained if the various types of pulmonary carcinomas are grouped. Table A7 presents his groupings of the specific histologic types. Using this classification as a basis for analysis of lung cancer sex-ratios in Norway, Kreyberg has observed that Group I carcinomas are significantly more frequent among males while Group II carcinomas show an approximately equal distribution among males and females. The author considers the recent rise in lung cancer in Norway to be a reflection of the increased prevalence of Group I carcinomas. Table 8 presents a summary of Kreyberg's investigation concerning 793 male and female cases of lung cancer. Among both males and females, the risk ratio among smokers is substantially higher for Group I types than for those of Group II. However, adenocarcinoma among males shows a risk ratio of 2.9, signifying a relationship with smoking. Kreyberg attributes the lower rates noted among females to their significantly lower consumption of tobacco in all forms.

TABLE 6.—*Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1]

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results			Comments
Wynder and Graham, 1950, U.S.A. (*316*).	644 autopsies on males with confirmed lung cancer.	*Percent cases by histologic type and smoking history*			The percentage of chain smokers in the general population (7.6) was significantly less than among the patients with adenocarcinoma. The authors refrained from making any definite conclusions due to the insufficient number of cases.
			All lung cancers other than adenocarcinoma (605)	*Adenocarcinoma (39)*	
		Nonsmokers	1.3	10.3	
		Light cigarette smokers	2.3	7.7	
		Moderate	10.1	15.4	
		Heavy	35.2	38.5	
		Excessive	30.9	10.3	
		Chain	20.3	18.7	

Author, year, country, reference	Number of persons and case selection method	Results				Comments
Doll and Hill, 1952, England (*73*).	916 male and 79 female cases with histologically confirmed lung cancer.	*Percent patients with lung cancer by average amount smoked daily over 10 years*				No statistically significant difference was found between the amounts smoked by the patients in the different histological groups. Number of proven adenocarcinomas too small for conclusions.
				Males		
			Epidermoid (475)	*Oat-cell or anaplastic (303)*	*Adenocarcinoma (33)*	
		Nonsmokers	0.2 (1)	0.7 (2)	6.1 (2)	
		Smokers:				
		<5 cigarettes/day	2.9 (14)	3.9 (12)	6.1 (2)	
		5–14	35.6 (169)	36.3 (110)	21.2 (7)	
		15–25	36.8 (175)	34.7 (105)	48.5 (16)	
		>25	24.4 (116)	24.4 (74)	18.2 (6)	
				Females		
			Epidermoid (18)	*Oat-cell or anaplastic (38)*	*Adenocarcinoma (10)*	Males—105 unclassified tumors. Females—13 unclassified tumors.
		Nonsmokers	61.1 (11)	31.6 (12)	50.0 (5)	
		Smokers:				
		<5 cigarettes/day	5.6 (1)	15.8 (6)	20.0 (2)	
		5–14	22.2 (4)	23.7 (9)	10.0 (1)	
		15–25	5.6 (1)	18.4 (7)	...	
		>25	5.6 (1)	10.5 (4)	20.0 (2)	

TABLE 6. *Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1] *(cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results					Comments
Breslow et al., 1954, U.S.A. (*42*).	493 male and 25 female cases with histologically proven lung cancer. 518 age and sex-matched controls.	*Percent of patients with specific lung cancers by tobacco usage during the 20 years prior to study*					Nonsmokers include pipe and cigar smokers only. The authors conclude that cigarette smoking appears to affect the development of epithelial carcinoma more than that of adenocarcinoma.
			All lung cancers other than adenocarcinoma (*472*)	*Adenocarcinoma* (*46*)		*Controls* (*518*)	
		Nonsmokers	5.9	13.0		24.4	
		Cigarette smokers	94.1	87.0		75.6	
Schwartz et al., 1957, France (*247*).	430 male and female cases with histologically confirmed lung cancer. 4 matched control groups.	*Percent of smokers by histologic type and smoking history*					† Difference significant at p≦0.05 level.
			Epidermoid	*Anaplastic*	*Unknown type*	*Cylindrical*	
		Cases	96.0	97.0	96.0	100.0	
		Controls	79.0†	83.0†	79.0†	96.0	
Haenszel et al., 1958, U.S.A. (*113*).	158 female cases of lung cancer.	*Relative risk for specified tumors (smokers/nonsmokers)*					134 cases with final histological determination. † Difference from unity significant at p≦0.01.
			Group I (Kreyberg)	*Adenocarcinoma*			
		Adjusted for age and occupation	3.0†	1.19			
Haenszel and Shimkin, 1962, U.S.A. (*112*).	2,191 male cases of lung cancer with adequate histologic data.	*Standardized mortality ratios*					Cases obtained from a 10 percent sample of lung cancer deaths in U.S.A. during 1958. The authors noted an absence of important differentials by histologic type.
			Epidermoid and undifferentiated carcinomas	*Adenocarcinoma*			
		White males total	100	100			
		Never smoked	6	18			
		Ex-smokers	34	46			
		<1 pack/day	123	116			
		>1 pack/day	499	467			

TABLE 6.—*Epidemiologic and pathologic investigations concerning smoking and the histology of lung cancer*[1] (*cont.*)

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of persons and case selection method	Results					Comments
Cohen and Hossain, 1966, U.S.A. (*58*).	417 male and female cases of lung cancer with histologic diagnosis 1939-63 at one hospital.		*Percent cases by histologic type and smoking history (number of smokers)*				The authors also noted that: 1. Adenocarcinomas were 2½-3 times more common in women 2. Only 1 percent of Kreyberg Group I cases were nonsmokers.
			Squamous	*Undifferentiated*	*Adenocarcinoma*	*Alveolar*	
		Nonsmokers	1.0 (3)	10.0 (17)	23.0 (8)	20.0(1)	
		Smokers	89.0(183)	90.0(145)	60.0(20)	...	
Ashley and Davies, 1967, England (*6*).	442 male and female cases of histologically diagnosed lung cancer.		*Percent cases by histologic type and smoking history*				The authors noted that cigarette smoking appears to be as strongly related to adenocarcinoma as to the other 2 types. Ashley's data on total number of cigarette smokers are inconsistent with his breakdown of smokers into groups based on number of cigarettes smoked per day.
			Undifferentiated	*Squamous*	*Adenocarcinom*		
		Nonsmokers	2.8 (4)	2.5 (6)	3.4 (2)		
		Pipe	9.9 (14)	9.9 (24)	1.7 (1)		
		Cigarette	87.3(124)	87.6(211)	94.9(56)		
		<10/day	14.1 (20)	22.4 (54)	22.0(13)		
		10-20	33.8 (48)	41.5(100)	33.9(20)		
		21-30	12.0 (17)	21.6 (52)	16.9(10)		
		31-40	14.1 (20)	12.9 (31)	8.5 (5)		
		>40	7.1 (10)	6.2 (15)	5.1 (3)		
Ormos et al., 1969, Hungary (*204*).	118 male and female cases of histologically proven lung cancer with adequate smoking information.		*Percent cases by histologic type and smoking history*				The author noted that the small number of cases allows for no definite conclusions.
			Group I	*Group II and large cell carcinomas*			
		Nonsmokers	21.0(18)	36.0 (9)			
		Smokers	79.0(68)	64.0(16)			

[1] Data obtained from patient interview and other sources.

TABLE 8.—*Tumor prevalence among males and females 35–69 years of age, by type of tumor and smoking category*

(Smokers constituted 85 percent of populations studied)

Sex and type of tumor	Smoking category			Expected number among smokers [1]	Risk ratio among smokers
	Total	Smoking all methods	Non-smokers		
Males					
Epidermoid carcinoma	434	431	3	17.0	25.4
Small cell anaplastic carcinoma	117	116	1	5.7	20.4
Adenocarcinoma	88	83	5	28.3	2.9
Bronchiolol-alveolar carcinoma	....	....	...	....	....
Carcinoid	46	39	7	39.7	1.0
Bronchial gland tumor	....	....	...	....	....
Total	685	669	16	90.7	7.4
Females					
Epidermoid carcinoma	12	9	3	.75	12.0
Small cell anaplastic carcinoma	8	5	3	.75	6.6
Adenocarcinoma	56	14	42	10.5	1.3
Bronchiolol-alveolar carcinoma	....	....	...	....	....
Carcinoid	32	7	25	6.3	1.1
Bronchial gland tumor	....	....	...	....	....
Total	108	35	73	18.3	1.9

[1] Number that would be expected if incidence rate among smokers were equal to that of nonsmokers.

SOURCE: Kreyberg, L. (*154*)